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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	16

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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1- File Copy

*U.S. GPO: 1998-437-638/80022

Office Action Summary	Application No. 08/973,021	Applicant(s) rsen, Mouritsen, Hindersson, Duch, Sorensen, Da
	Examiner WILLIAM SANDALS	Group Art Unit 1636

X Responsive to communication(s) filed on *Feb 23, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-42* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

X Claim(s) *1-42* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

X Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Response to Arguments

2. Applicant's have argued in Paper No. 13, filed February 1, 1999, that the rejection of claims 1-2, 4-5, 8-11, 15-16, 20, 22-24 and 27 under 35 USC 102(e) is improper since the Kay et al. reference does not teach the method of transduction of viral vectors into eukaryotic hosts where delivery of "one gene to one cell" is possible.

Applicant's attention is drawn to column 23, lines 1-8 where Kay et al. teaches that the method may be practiced with viral vectors such as vaccinia, adenovirus and retrovirus in a eukaryotic host. While Kay et al. do not teach one of skill in the art the specifics of how to practice the invention with viral vectors in eukaryotic hosts, it is well known to one of skill in the art would how to practice the invention with viral vectors to deliver "one gene to one cell" as taught for instance in Sigmund, C., Hypertension, Vol. 22(4):599-608 (see especially the abstract and page 602). Since this knowledge is well known to one of skill in the art, the specific teachings of what is well known in the art as recited in Sigmund, C. is proper to be used in support of the rejection made under 35 USC 102.

3. Regarding the citation of Sigmund, C., please see the MPEP at section 2121.01. In cases such as this where the "Use of Prior Art in Rejections Where Operability Is in Question: A REJECTION IS APPROPRIATE IF ONE OF ORDINARY SKILL COULD PRACTICE THE CLAIMED INVENTION GIVEN THE TEACHINGS OF THE REFERENCE COMBINED WITH KNOWLEDGE IN THE ART"

"In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention `not novel' or `anticipated' within section 102, the stated test is whether a reference contains an `enabling disclosure'... ." In re Hoeksema,158 USPQ 596 (CCPA 1968). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue , 226 USPQ 619 (Fed. Cir. 1985).

(a) 35 U.S.C. 102 Rejections and addition of evidence showing reference is operable SECONDARY EVIDENCE SHOWING REFERENCE CONTAINS AN "ENABLING DISCLOSURE" CAN BE COMBINED WITH THE REFERENCE TO MAKE OUT A 35 U.S.C. 102 REJECTION

It is possible to make a 35 U.S.C. 102 rejection even if the reference does not itself teach one of ordinary skill how to practice the invention, i.e., how to make or use the article disclosed. If the reference teaches every claimed element of the article, secondary evidence, such as other patents or publications, can be cited to show public possession of the method of making and/or

using. In re Donohue, 226 USPQ 619, 621 (Fed. Cir. 1985). See MPEP § 2131.01 for more information on 35 U.S.C. 102 rejections using secondary references to show that the primary reference contains an "enabling disclosure."

4. Therefore, citing Sigmund, C. as a demonstration of the well known use of retroviral vectors to deliver "one gene to one cell" as set forth in applicant's arguments is proper, and establishes the enablement of the Kay et al. reference with regard to the use of viral vectors in the practice of the method of Kay et al. as it anticipates applicants claimed invention.

5. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., non-ligand based detection of a phenotype) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

6. The rejection of claims 1-2, 4-5, 8-11, 15-16, 20, 22-24 and new claims 30-31, 35-37 and 39-42 under 35 USC 102(e) is repeated below.

7. Applicant's have argued that the rejection of claims 6-7, 12-14, 17-19 and 21 under 35 USC 103(a) lacks proper motivation where the motivation statement set forth that Kay et al.,

Burke et al. and Wong et al. were all investigating a "key element" of the claims. Responses to the arguments pertaining to the rejection are included in the repeated rejection below.

8. Applicant's have noted that claims 25-26 were not rejected over prior art. This oversight has been corrected, and the rejection of claims 25-26 has been included below.

9. Applicants have sent a letter to address the rejection of claim 7 under 35 USC 103(a). While the letter addresses certain facts pertaining to the authorship of the Lund et al. reference, the only way to properly overcome the rejection is to file a declaration under 37 CFR 1.131 or 37 CFR 1.132.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Section "(c)" of the claim is drawn to "screening said transduced cells to see

whether some of them have altered a preselected phenotypic trait, wherein the screening method is different from capture of the expressed ribonucleic acid(s) or peptide(s) with a ligand". The limitation of "wherein the screening method is different from capture of the expressed ribonucleic acid(s) or peptide(s) with a ligand" is new matter, since nowhere in the original claims or specification is this element taught or set forth.

12. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Section "(c)" of the claim is drawn to "screening said transduced cells to see whether some of them have altered a preselected phenotypic trait, where alteration of the preselected phenotypic trait in a cell is ascribable to the expressed ribonucleic acid(s) or peptide(s) affecting biological functions of the cell which have influence on the preselected phenotypic trait". The limitation of "where alteration of the preselected phenotypic trait in a cell is ascribable to the expressed ribonucleic acid(s) or peptide(s) affecting biological functions of the cell which have influence on the preselected phenotypic trait" is new matter, since nowhere in the original claims or specification is this element taught or set forth.

13. Claim 34 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Section "(c)" of the claim is drawn to "screening said transduced cells to see whether some of them have altered a preselected phenotypic trait, which indicates that peptide(s) encoded by DNA sequence(s) are bound to MHC molecules on the surface of the transduced cells". The limitation of " which indicates that peptide(s) encoded by DNA sequence(s) are bound to MHC molecules on the surface of the transduced cells" is new matter, since nowhere in the original claims or specification is this element taught or set forth.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 33 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. In claim 33, section "(c)" of the claim is drawn to "screening said transduced cells to see whether some of them have altered a preselected phenotypic trait, where alteration of the preselected phenotypic trait in a cell is ascribable to the expressed ribonucleic acid(s) or peptide(s) affecting biological functions of the cell which have influence on the preselected phenotypic trait".

No nexus is provided in the claims or specification to inform one of ordinary skill in the art how to know when a phenotypic trait is ascribable to the expressed ribonucleic acid(s) or peptide(s) where they may affect biological functions of the cell. Lacking this guidance, the claim is vague and indefinite.

17. In claim 34, section "(c)" of the claim is drawn to "screening said transduced cells to see whether some of them have altered a preselected phenotypic trait, which indicates that peptide(s) encoded by DNA sequence(s) are bound to MHC molecules on the surface of the transduced cells".

No nexus has been provided to guide one of ordinary skill in the art by the claims or specification to know how the altered, preselected phenotypic trait would produce the effect which indicates that peptide(s) encoded by DNA sequence(s) are bound to MHC molecules on the surface of the transduced cells". Lacking this guidance, the claim is vague and indefinite.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 1-2, 4-5, 8-11, 15-16, 20, 22-24, 30-31, 35-37 and 39-42 are rejected under 35 U.S.C. 102(e) as being anticipated by Kay et al.

The claims are drawn to a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from; (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to sequences encoding purification tags, (d) sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a), (b), (c) or (d) are expressed in cells and produce a phenotypic alteration in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be glycosylated. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis, which may encode a random peptide of 6-10, or 8-9 amino acids in length. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences. The vector may be amplified by PCR prior to the transfection step. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein

may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule.

Kay et al. taught (see especially columns 3-6, 16-18, 22-24, and 28) a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from; (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to sequences encoding purification tags, (d) sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a), (b), (c) or (d) are expressed in cells and produce a phenotypic alteration in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be glycosylated. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule. The RNA or peptide identified by the method may be a lead compound. The RNA or peptide identified by the method may be a lead compound. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis, which may encode a random peptide of 6-10, or 8-9 amino acids in length. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences. The vector may be amplified by

PCR prior to the transfection step. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule. Kay et al. taught each and every aspect of the instant invention, thereby anticipating Applicant's invention.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 6, 12-14, 17-19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. in view of Burke et al and Wong et al.

The claims are drawn to a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from; (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to sequences encoding purification tags, (d) sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a),

(b), (c) or (d) are expressed in cells and produce a phenotypic alteration in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis, where the ends of the PCR product may be trimmed by 3'-5' exonuclease. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences, where the heterologous ends may contain two different promoters, and where a CMV promoter may replace the 5' LTR. The viral vector may be introduced into the cell by non-viral transfection methods. The vector may be amplified by PCR prior to the transfection step. The host cell may be a viral packaging cell which has been transfected with a vector expressing a single transcript consisting of gag-pol, a drug resistance gene and the env gene. The packaging cell may be a semi-packaging cell line which has been transfected with a minivirus vector. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule.

The partly random sequences may encode glycosylation sites or anchor residues, or signal sequences or leader sequences or recognition sequences, which may direct the fusion proteins to defined cellular compartments.

Kay et al. taught (see especially columns 3-6, 16-18, 22-24, and 28) a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from; (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to sequences encoding purification tags, (d) sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a), (b), (c) or (d) are expressed in cells and produce a phenotypic alteration in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule.. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences. The vector may be amplified by PCR prior to the transfection step. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a

protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule.

Kay et al. did not teach that the ends of the PCR product may be trimmed by 3'-5' exonuclease nor that the vectors may contain two different promoters, and where a CMV promoter may replace the 5' LTR. The viral vector may be introduced into the cell by non-viral transfection methods. Also not taught was that the host cell may be a viral packaging cell which has been transfected with a vector expressing a single transcript consisting of gag-pol, a drug resistance gene and the env gene. The packaging cell may be a semi-packaging cell line which has been transfected with a minivirus vector.

Burke et al. taught (see especially columns 1-6) that the viral vector in an expression library contained partially random DNA sequences which encoded leader sequences and anchor sequences for fusion proteins, where the sequences were glycosylated and also leader sequences which directed the fusion proteins to specific cellular compartments.

a) Applicants have argued here that Burke et al. did not teach totally random DNA sequences. This is correct and the above paragraph has been appropriately amended. Burke et al. is cited to demonstrate the well known use of leader sequences and anchor sequences for fusion proteins, and where they demonstrated that these sequences may be glycosylated by the host cell.

Wong et al. taught (see especially the abstract and introduction, materials and methods and the Figures) the well known use of a 3'-5' exonuclease to blunt end inserts for ligation into a

vector, the inclusion of an antibiotic marker gene into a vector and the incorporation of a strong promoter such as the CMV promoter into a viral vector in order to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kay et al., Burke et al and Wong et al. to produce the instant claimed invention because Kay et al. taught the use of a library of random DNA sequences which would act as expressed tags for identification when linked to coding sequences for proteins of interest, or as leader sequences, anchors or sites for post-translational modification. Kay taught the use of viral vectors for the expression libraries, and the use of antibodies and antibody components as fusion proteins with random sequences as described above where the translated proteins and transcribed RNA's were used to detect alterations in the phenotype of the host cell. Burke et al. taught the use of random sequences linked to sequences encoding proteins to produce fused leader sequences, "tags", and post-transcriptional and post-translational modifications of the fused polypeptides to identify vector induced alterations in the phenotype of the host cell. Wong et al. taught the modification of inserts in viral vectors to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Kay et al., Burke et al and Wong et al. to produce the instant claimed invention because Kay et al. taught the use of a library of random DNA sequences which would act as expressed tags for identification when linked to coding sequences for proteins

of interest, or as leader sequences, anchors or sites for post-translational modification. Kay taught the use of viral vectors for the expression libraries, and the use of antibodies and antibody components as fusion proteins with random sequences as described above where the translated proteins and transcribed RNA's were used to detect alterations in the phenotype of the host cell. Burke et al. taught the desirable use of random DNA sequences linked to DNA sequences encoding proteins to produce fused leader sequences, "tags", and post-transcriptional and post-translational modifications of the fused polypeptides to identify vector induced alterations in the phenotype of the host cell. Wong et al. taught the modification of inserts in viral vectors to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell. Since all of the references taught a key element of the instant claimed invention which is the detection of an altered phenotype in a host cell, it would have been obvious to combine these references to produce the instant claimed invention. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Kay et al., Burke et al and Wong et al.

b) Applicants have argued that motivation to combine the references was insufficient. Since Burke et al. was cited to provide evidence of the well known teachings of viral vector in an expression library which contained partially random DNA sequences which encoded leader sequences and anchor sequences for fusion proteins, where the sequences were glycosylated and also leader sequences which directed the fusion proteins to specific cellular compartments. Wong et al. was cited to provide evidence of the well known use of a 3'-5' exonuclease to blunt end

inserts for ligation into a vector, the inclusion of an antibiotic marker gene into a vector and the incorporation of a strong promoter such as the CMV promoter into a viral vector in order to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell. Kay et al. provided the basis for the rejection in its teachings of the use of random oligonucleotides which encoded and expressed small RNAs and peptides on the surface of cells for the purpose of identifying the functional aspects of the small RNAs and peptides. Burke et al. and Wong et al. merely provided evidence of teachings well known in the art. A nexus to the teachings of Kay et al. where they were all investigating a "key element" of the claimed invention is sufficient to provide motivation to combine the teachings to produce the instant claimed invention.

22. Claim 7 rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al, Burke et al. and Wong et al. as applied to claims 6, 12-14, 17-19 and 21 above, and further in view of Lund et al.

The claims are drawn to all the limitations above and to a method of temperature-cycling ligation.

The claims are rejected for all the reasons recited above and because Lund et al. taught (see the entire article) a method of temperature-cycling ligation.

The priority date of the instant claim is the date of filing of the PCT Application No. PCT/DK96/00231, filed May 5, 1996, because upon inspection of the Danish priority document

DK0629/95, filed June 2, 1995, no mention of the method of temperature-cycling ligation has been found. The publication date of the Lund et al. reference is March 1, 1996, which establishes this reference as prior art.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kay et al., Burke et al. and Wong et al. with Lund et al. because the Kay et al., Burke et al. and Wong et al. taught the use of ligation chain reaction to amplify a desired DNA prior to insertion of the desired DNA into a vector, and Lund et al. taught an improved method of use of ligation chain reaction to amplify a desired DNA prior to insertion of the desired DNA into a vector.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Kay et al., Burke et al. and Wong et al. with Lund et al. because the Kay et al., Burke et al. and Wong et al. taught the use of ligation chain reaction to amplify a desired DNA prior to insertion of the desired DNA into a vector, and Lund et al. taught an improved method of use of ligation chain reaction to amplify a desired DNA prior to insertion of the desired DNA into a vector. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Kay et al., Burke et al., Wong et al. and Lund et al.

23. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. in view of Burke et al and Wong et al. as applied to claims 6, 12-14, 17-19 and 21 above, and further in view of Stemmer et al.

The claims are as described above and are also drawn to the screening wherein T-cell epitopes bound to MHC molecules are present on the surface of transduced cells, which may be a phenotypic trait.

Stemmer et al. taught (see especially the abstract, the summary of the invention, column 10, lines 20-29, column 13, lines 21-31 and column 14, lines 27-32) the expression of random peptides which are T-cell epitopes, which are presented on MHC molecules on the surface of transduced host cells, which may be a phenotypic trait.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kay et al. Burke et al and Wong et al. with Stemmer et al. because Kay et al. taught the basis for the rejection in its teachings of the use of random oligonucleotides which encoded and expressed small RNAs and peptides on the surface of cells for the purpose of identifying the functional aspects of the small RNAs and peptides. Stemmer et al. were investigating the use of random oligonucleotides which encoded and expressed small RNAs and peptides on the surface of cells for the purpose of identifying the functional aspects of the small RNAs and peptides, just as was Kay et al. Stemmer et al. states that "it would be advantageous to develop a method which allows for the production of large libraries of mutant DNA, RNA or proteins and the selection of particular mutants for a desired goal". Kay et al.

states "the invention provides a rapid and easy way of producing a large library that results in a plurality of longer proteins, polypeptides and/or peptides that can efficiently be screened to identify those with novel and improved binding specificities, affinities and stabilities for a given ligand of choice". Thus it is clear that Kay et al. and Stemmer et al. were motivated to identify similar binding ligands which were made from random short DNA's encoding short peptides and polypeptides of interest, where Stemmer et al. were investigating a subset of the teachings of Kay et al. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Kay et al. Burke et al and Wong et al., and Stemmer et al.

Conclusion

24. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

March 19, 1999

NANCY DEGEN
PRIMARY EXAMINER